Dicarba-*closo*-dodecarborane-containing half-sandwich complexes of ruthenium, osmium, rhodium and iridium: Biological relevance and synthetic strategies

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This review describes how the incorporation of dicarba-*closo*-dodecarboranes into half-sandwich complexes of ruthenium, osmium, rhodium and iridium might lead to the development of a new class of compounds with applications in medicine. Such a combination not only has unexplored potential in traditional areas such as Boron Neutron Capture Therapy agents, but also as pharmacophores for the targeting of biologically important proteins and to the development of targeted drugs. The synthetic pathways used for the syntheses of dicarba-*closo*-dodecarboranes-containing half-sandwich complexes of ruthenium, osmium, rhodium and iridium are also reviewed. Complexes with a large variety of geometries and characteristics can be prepared. Examples of addition reactions on the metal centre, B–H activation, transmetalation reactions or direct formation of metal–metal bonds are discussed.

Introduction

Half-sandwich complexes of ruthenium, osmium, rhodium and iridium are a versatile class of organometallic compounds. Their accessibility, robustness, air-stability and water-solubility are examples of the unique properties that allow their applications in various fields of chemistry such as in synthesis and catalysis,[1] or as building blocks in supramolecular chemistry.[2] Their biological behaviour as anticancer drugs is also highly promising.[3] During the last 10 years, half-sandwich arene and cyclopentadienyl complexes[4] of Ru^{II},[5] Os^{II},[6] Rh^{III},[7] and Ir^{III},[8] for example, have all shown promise as antitumoural and/or antimetastatic candidates, and structure-activity relationships guiding new design concepts have begun to emerge.[9]

Clusters containing boron and carbon, termed carbaboranes, are a class of compounds that possess different sizes, architectures, charges and dipole moments.[10] Among them, icosahedral dicarba-*closo*-dodecarboranes ($C_2B_{10}H_{12}$) were first reported in 1963.[11] Three isomers, 1,2- 1,7- and 1,12-dicarba-*closo*-dodecarboranes (or *ortho*, *meta* and *para*-dicarba-*closo*-dodecarboranes), exist depending on the positions of the two carbon atoms. The molecular geometry of *o*, *m* and *p*-dicarba-*closo*-dodecarboranes with the IUPAC numbering of the cage atoms[12] are shown together in Figure 1.

The carbon and boron atoms in these polyhedral clusters are hypercoordinated (hexacoordinated) which leads to the formation of 20 triangular faces.[13] The hexacoordination of the carbon and boron atoms of dicarba-*closo*-dodecarboranes is due to the delocalisation of the 26 skeletal electrons through the entire structure of the clusters.[14] This delocalisation and the resulting electron-deficient bonding leads to the spreading of the bonding power of a pair of electrons over more than two atoms.[15] The aggregation of atoms in 3-centre-2-electron bonding compensates for this low electron density.

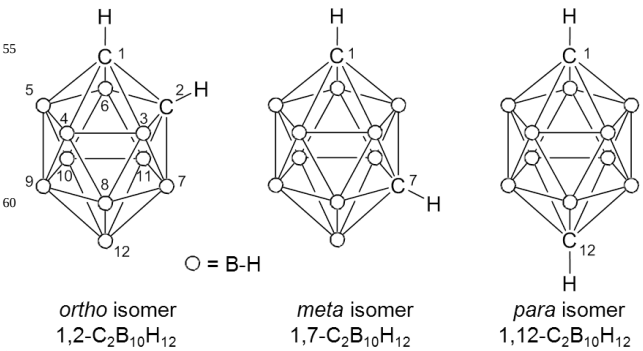


Figure 1. Molecular geometry of *o*, *m* and *p*-dicarba-*closo*-dodecarboranes.[12]

Beyond these non-classical bonding interactions, dicarba-*closo*-dodecarboranes possess unusual properties, including high symmetry and remarkable stability; these properties have given rise to numerous applications. For example, dicarba-*closo*-dodecarborane compounds have been used as building blocks in various systems, such as dendrimers,[16] polymers,[17] and nanoparticles.[18] The weakly acidic character of the CH groups of these clusters of boron and carbon allows their chemical functionalization.[19] Thus, various molecules containing dicarba-*closo*-dodecarboranes along with analogues of biomolecules have been reported and have found biochemical applications.[20] Indeed, dicarba-*closo*-dodecarborane cages are high-boron-content molecules and they are stable under physiological conditions.[21] They are ideally suited for boron neutron capture therapy (BNCT),[22] but also have potential in other fields of drug discovery, molecular imaging, and targeted radionuclide therapy.[23]

The combination of the remarkable properties of half-sandwich complexes with the unique features of dicarba-

closo-dodecarborane clusters therefore results in interesting new molecules.[24] Applications of these in organometallic synthesis, catalysis, or bioinorganic chemistry, for example, can be envisaged. Here we review the potential that incorporation of these dicarba-*closo*-dodecarboranes into half-sandwich complexes of ruthenium, osmium, rhodium and iridium could present in terms of biological applications. Based on the unusual properties of both dicarba-*closo*-dodecarboranes and half-sandwich complexes, some potential applications in medicine are proposed and explored. Then, reported strategies for the synthesis of dicarba-*closo*-dodecarborane-containing half sandwich complexes of ruthenium, osmium, rhodium and iridium are described.

1. Why combine dicarba-*closo*-dodecarboranes and half-sandwich complexes?

1.A. To increase the selectivity of dicarba-*closo*-dodecarboranes as BNCT agents.

Boron neutron capture therapy (BNCT) is the traditional area of application of dicarba-*closo*-dodecarborane molecules in medicine. This binary method consists of the nuclear reaction of nontoxic and nonradioactive ^{10}B atoms and low-energy thermal neutrons that produces high-energy $^{4}He^{2+}$ α-particles and $^{7}Li^{3+}$ ions. The dissipation of the high kinetic energy of these particles is achieved in a small distance (less than one cell diameter), which allows accurate destruction of the targeted cells. Therefore, the efficiency of this therapy depends on the number of boron atoms delivered to cancer cells, while the selectivity strongly depends on the preferential accumulation of boron in tumour tissues rather than in normal tissues, as well as on the low general cytotoxicity of the compounds.[25] Dicarba-*closo*-dodecarboranes contain ten boron atoms; they possess a rather low cytotoxicity and these clusters are extremely stable in biological medium. These characteristics explain why dicarba-*closo*-dodecarborane clusters have the potential to be efficient BNCT agents. However, dicarba-*closo*-dodecarborane clusters on their own do not possess the ability to selectively target cancer cells.

To increase the selectivity of dicarba-*closo*-dodecarboranes towards cancer cells and therefore to increase the clinical feasibility of boron neutron capture therapy, various approaches have been developed. A first strategy to obtain selectivity towards cancer cells is to attach borane clusters to cellular building blocks. Indeed, most solid tumours are known to possess a hypervasculature, a defective vascular architecture, and an impaired lymphatic drainage.[26] Thus, while the normal endothelial layer surrounding the blood vessels feeding healthy cells restricts the amount of constituents necessary for cell replication (amino acids and nucleic acid precursors for example), the endothelial layer of blood vessels in diseased tissues allows an elevated quantity of such cell constituents to enter the cells.[23, 27] Another strategy is to attach the borane cluster to tumour antibodies that can target specific cell types.[28] A third approach is to use nano-containers such as lipoproteines and liposomes.[29] Encapsulation of hydrophilic borane compounds in aqueous cores of liposomes, or incorporation of boron-containing lipids in liposome bilayers leads to a selective delivery of BNCT therapeutics to tumours.

On the other hand, mononuclear arene ruthenium complexes are known to target DNA and RNA[30] but they are also able to bind biomolecules such as the sulphur-containing amino acids *L*-cysteine and *L*-methionine[31] and imidazole-containing amino acid *L*-histidine,[32] for example. Thus, the attachment of dicarba-*closo*-dodecarborane clusters to arene ruthenium half-sandwich complexes able to bind cellular building blocks could result in an increase of the selectivity of dicarba-*closo*-dodecarboranes towards cancer cells. Moreover, the synthetic diversity of the arene ligand provides an excellent scaffold for the coupling of organic segments for targeted chemotherapy.[33] The selectivity for cancer cells of arene ruthenium complexes has been shown to be dependent on ligands surrounding the metal centre. For example, the water-soluble phosphine ligand 1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1]decane (pta) seems to play a significant role in the selectivity of the RAPTA-C [*p*-cymRu(pta)Cl_2] (*p*-cym = *para*-cymene) complex.[34] Therefore, the combination of nontoxic, highly stable and high-boron content dicarba-*closo*-dodecarborane molecules with low toxic biomolecule-containing complexes could result in the synthesis of BNCT agents possessing a high selectivity for cancer cells.

1.B. To diversify the scope of biological applications of half-sandwich complexes.

The medicinal chemistry of dicarba-*closo*-dodecarboranes covers a much broader field than the niche of boron neutron capture therapy.[21, 25, 28] The unique properties of these molecules have found application in radionuclide diagnostics, for example. Indeed, due to the high stability of dicarba-*closo*-dodecarboranes under *in vivo* conditions, the labelling of these clusters by radionuclides affords compounds that resist degradation better than conventional organic molecules.[28] The labelling of dicarba-*closo*-dodecarborane derivatives with radioactive isotopes such as ^{99}Tc, ^{57}Co and ^{73}Se allows the determination of compound distribution by various techniques, including positron emission tomography (PET) and magnetic resonance imaging (MRI). These imaging techniques, currently under investigation,[35] could be applied to the study of the mechanisms of action of half-sandwich complexes. Utilisation in radionuclide therapy of such complexes could also be considered after functionalization of the arene unit with antibodies to enhance the selective delivery of radionuclides into cancer cells, for example.

Another potential interest in the combination of dicarba-*closo*-dodecarboranes and half-sandwich complexes of ruthenium, osmium, rhodium and iridium for biological applications lies in the spherical geometry, the steric hindrance and the very strong hydrophobic character of dicarba-*closo*-

dodecarboranes:[36] Indeed, a dicarba-*closo*-dodecarborane molecule has a diameter of about 1 nm and a volume approximately 40% larger than the volume of a rotating phenyl group.[14] The degree of potential functionalization of dicarba-*closo*-dodecarboranes being much higher than that of phenyl rings, dicarba-*closo*-dodecarboranes are considered as convincing bioisosteres for aryl, cycloalkyl or adamantyl units. For instance, this approach has been used by Valliant and co-workers to synthesise an analogue compound of tamoxifen in-which the A phenyl group has been substituted by an *o*-dicarba-*closo*-dodecarborane unit.[37]

On the other hand, the hydrophobic arene and cyclopentadienyl ligands and the hydrophilic metal centres give amphiphilic properties to the arene/cyclopentadienyl metal units. This amphiphilic behaviour has been one of the major reasons to the development of arene-ruthenium-based anticancer drugs.[3e] Therefore, the utilisation of dicarba-*closo*-dodecarboranes as ligands presenting both steric and hydrophobic unusual effects could increase the bioavailability and the cytotoxicity of half-sandwich complexes of ruthenium, osmium, rhodium and iridium.

1.C. To provide half-sandwich complexes with useful dicarba-*closo*-dodecarborane spectroscopic probes.

1.C.1. Raman and infrared spectroscopy.

Dicarba-*closo*-dodecarboranes introduce useful and characteristic probe properties that can be utilised not only for the characterisation of the complexes incorporating boron cluster ligands but also for the determination of interactions between these and biomolecules.

The Raman and IR spectra of the three dicarba-*closo*-dodecarborane isomers are very similar, (see Figure 2 for the corresponding spectra of solid *p*-dicarba-*closo*-dodecarborane). The infrared spectra of these boron clusters contain a strong and broad absorption band at around 2600 cm^{-1} due to B−H stretching vibrations. Along with this absorption, an intense Raman line is also observed in the region of 760 cm^{-1}.[38] The fact that some bands are active only in Raman spectroscopy and some others only in IR spectroscopy implies that both IR and Raman spectra should be measured to collect the full information given by vibrational spectroscopy.

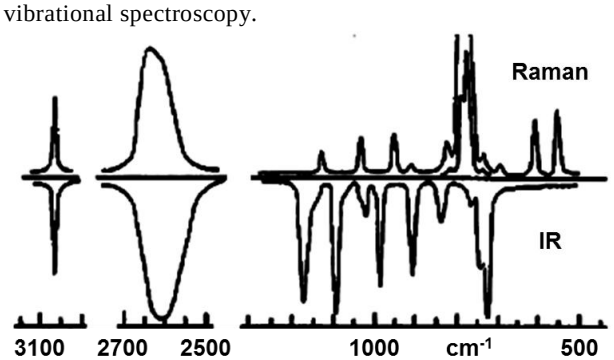


Figure 2. FT-IR and Raman spectra of solid *p*-dicarba-*closo*-dodecarborane. Adapted with permission from ref. 38. Copyright (1992) American Chemical Society.

The very characteristic Raman stretching signal of B–H at around 2600 cm^{-1} allows the utilisation of dicarba-*closo*-dodecarboranes as Raman reporters and biological probes. Indeed, this signal is in a spectroscopically silent region of cells. This vibrational property has been recently used by Pezacki and co-workers in studies of the functionalization of silver nanoparticles by 1-thiol-*o*-dicarba-*closo*-dodecarborane, followed by functionalization with an antibody.[39] Combination of dicarba-*closo*-dodecarboranes with surfaces and nanoparticles can lead to compounds presenting enhanced Raman properties,[40] while the functionalization with antibodies provides a strong selectivity for targeted cancer cells. Surface-Enhanced Raman Scattering (SERS) microscopy has been used to demonstrate tumour cell targeting of this nanostructure as well as the delivery of a high concentration of boron atoms into targeted cancer cells.[39] Figure 3 shows Raman spectra of 1-thiol-*o*-dicarba-*closo*-dodecarborane (a), of the dicarba-*closo*-dodecarborane labelled nanoparticle (b) and of a hot spot of a dicarba-*closo*-dodecarborane labelled nanoparticle on the human hepatoma Huh7.5 cell surface (c).

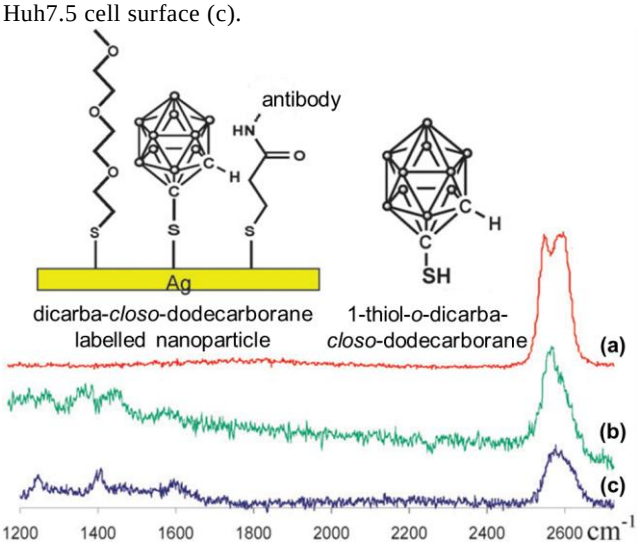


Figure 3. Raman spectra of 1-thiol-*o*-dicarba-*closo*-dodecarborane (a), of the dicarba-*closo*-dodecarborane labelled nanoparticle (b) and of a hot spot for a dicarba-*closo*-dodecarborane labelled nanoparticle on a cell surface (c). Reprinted with permission from ref. 39. Copyright (2009) Royal Chemical Society.

1.C.2. NMR spectroscopy.

Two isotopes of boron possess nuclear spin (^{11}B with spin quantum number I=3/2 and a natural abundance of 80.42%; ^{10}B with I=3 and a natural abundance of 19.58%). The ^{11}B NMR signals are broad (10-100 Hz) and the corresponding resonances are usually assigned with two-dimensional NMR techniques.

Due to the quadrupolar nature of ^{10}B and ^{11}B, the ^{1}H–B

couplings are rarely resolved in the ^{1}H NMR spectra of dicarba-*closo*-dodecarboranes (B−H signal protons are in the range -0.5 ppm to 2.5 ppm).[23] They can be considerably simplified by using ^{1}H NMR with ^{11}B decoupling (the signals for the protons coupled to ^{11}B are singlets while the signals for the protons coupled to ^{10}B are in the baseline). ^{1}H – ^{11}B HMQC and ^{11}B – ^{11}B COSY spectra are also used to assign the ^{1}H and ^{11}B spectra. Finally, the ^{1}H NMR resonances of the C−H protons are also broad (about 20 Hz), presumably due to geometric restrictions.

A standard ^{1}H NMR spectrum and a ^{1}H spectrum with ^{11}B decoupling of *o*-dicarba-*closo*-dodecarborane are shown in Figure 4a. Figure 4b illustrates the ^{1}H – ^{11}B HMQC spectrum of *o*-dicarba-*closo*-dodecarborane and ^{11}B – ^{11}B COSY of *o*-dicarba-*closo*-dodecarborane is given in Figure 4c.[41]

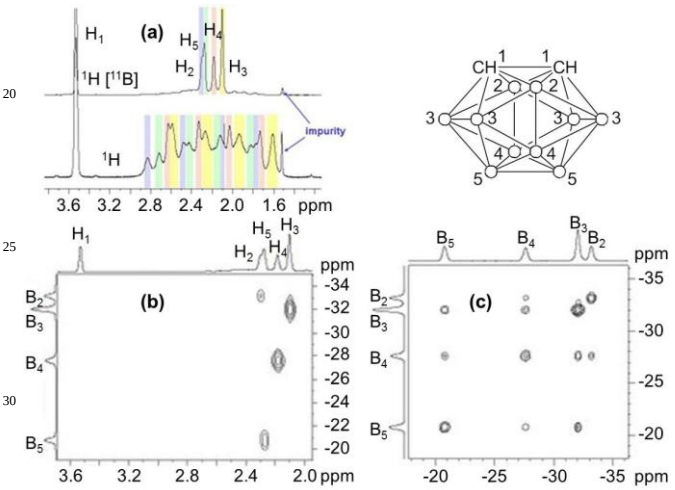


Figure 4. Standard ^{1}H NMR spectrum and ^{1}H spectrum with ^{11}B decoupling (a); ^{1}H – ^{11}B HMQC spectrum (b) and ^{11}B – ^{11}B COSY (c) of *o*-dicarba-*closo*-dodecarborane.[41]

1.C.3. Mass spectrometry.

Mass spectrometry is a method of choice for the identification of the isotopic compositions of carbaboranes. Indeed, the characteristic isotopic patterns of the two isotopes ^{11}B and ^{10}B can be used to obtain indirect information on the *nido* (B_9) or *closo* (B_{10}) structure of the cluster. Figure 5 shows simulations of the isotopic patterns of *closo*-*p*-1,12-$C_2B_{10}H_{12}$ and of the corresponding deboronated *nido*-anion 2,9-$C_2B_9H_{12}^-$.

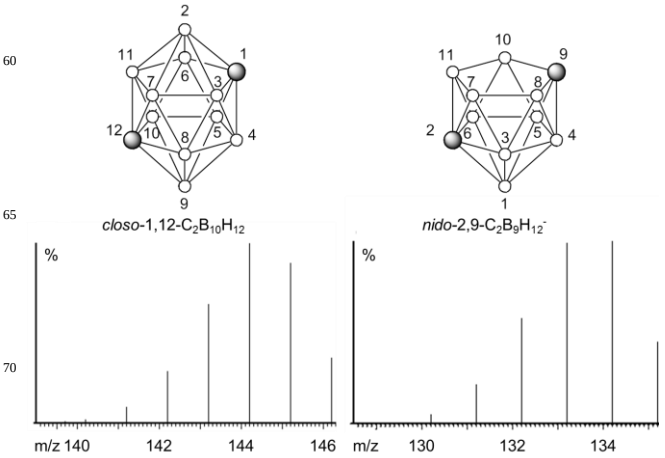


Figure 5. Simulations of the isotopic patterns of *closo*-*p*-1,12-$C_2B_{10}H_{12}$ and of the corresponding deboronated *nido*-anion 2,9-$C_2B_9H_{12}^-$.

The combination of dicarba-*closo*-dodecarboranes with half-sandwich complexes of ruthenium, osmium, rhodium and iridium can provide a distinct isotopic pattern depending on the nature of the metal centre.

1.D. To target specific proteins.

1.D.1. Estrogen and retinoid receptors.

Dicarba-*closo*-dodecarboranes and dicarba-*closo*-dodecarborane derivatives have been used as pharmacophores to enhance the hydrophobic interactions of pharmaceutical compounds with estrogen[42] and retinoid receptors.[43] The estrogen receptor (ER) agonist behaviour of these dicarba-*closo*-dodecarborane derivatives is of central importance.[44] Indeed, in ER positive tumours, such as in some breast cancers, the estrogen receptors are over-expressed which cause a cell proliferation and *in fine* an increase of the tumour size. In the meantime, an ER deficiency leads to a loss of bone mass due to the estrogenic regulation of bone maintenance.[23] Thus many efforts are focused on the synthesis of ER agonists and antagonists.

The X-ray structure of the human ligand binding domain (LBD) hERαLBD of the estrogen receptor has been determined.[45] LBD contains a phenolic unit, a hydrophobic cavity and a polar group such as an amine or alcohol. A molecule able to bind this domain should therefore present matching characteristics. Precisely, the phenolic 17β-estradiol, which is the endogenous ligand for estrogen receptor, bears a phenolic residue, an hydrophobic group adjacent to the phenolic ring, and another hydroxyl group located at a suitable position on the molecule, (see Figure 6a). Based on these considerations, in 1999 Endo and co-workers biologically evaluated compounds having phenolic ring, *m*-dicarba-*closo*-dodecarborane or *p*-dicarba-*closo*-dodecarborane as a hydrophobic moiety with a hydrophilic group on the dicarba-*closo*-dodecarborane cluster (alcohol, amine or carboxylic acid), (see Figure 6b for an example of

such molecules).[46]

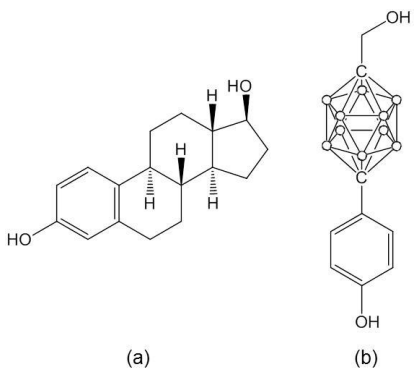


Figure 6. (a) Molecular structure of 17β-estradiol; (b) Molecular structure of a *p*-dicarba-*closo*-dodecarborane derivative.

These types of compounds are efficient ER agonists.[5] Structure–activity relationships have identified the key factors for the design of a library of potential ER binding ligands incorporating dicarba-*closo*-dodecarboranes.[23, 47] Docking simulations have also been performed[48] as well as *in vivo* experiments that demonstrate that the administration of such compounds to estrogen-deficient mice prevents bone loss as effectively as administration of 17β-estradiol.[23]

Retinoic acid is a natural metabolite of vitamin A that is involved in the regulating the development of normal and tumoral epithelial cells in various tissues.[49] The utilisation of retinoic acid as a clinical drug for the treatment of acute promyelocytic leukemia has been recently approved.[50] Retinoids are related compounds of retinoic acid able to bind and to activate specific nuclear retinoic acid receptors (RARs)[51] and retinoid X receptors (RXRs)[52] receptors. The resulting complexes act then as modulators for the target gene transcription.[53] The affinity between these ligands and their receptors is due to precise structural features,[51, 54] such as the presence of a carboxylic acid group linked to a hydrophobic pharmacophore by an appropriate spacer.[46]

In this context and following the same strategy developed for the estrogen receptor agonists, Endo and co-workers synthesised RARs and RXRs agonists containing the high hydrophobic dicarba-*closo*-dodecarborane units.[53] The structure-activity relationship demonstrated that for a same compound the bulky dicarba-*closo*-dodecarborane unit fits better the RAR cavity than the RXR cavity. This interesting difference of selectivity between dicarba-*closo*-dodecarboranes and RAR/RXR binding domains has been explained by docking simulations performed by Calvaresi and Zerbetto.[55] Indeed, for one of the two sites of interaction of dicarba-*closo*-dodecarborane with these LBDs, the dicarba-*closo*-dodecarborane unit matches the C_{12} region of RARs, while the C=C double bond region is targeted for RXRs, (see Figure 7).

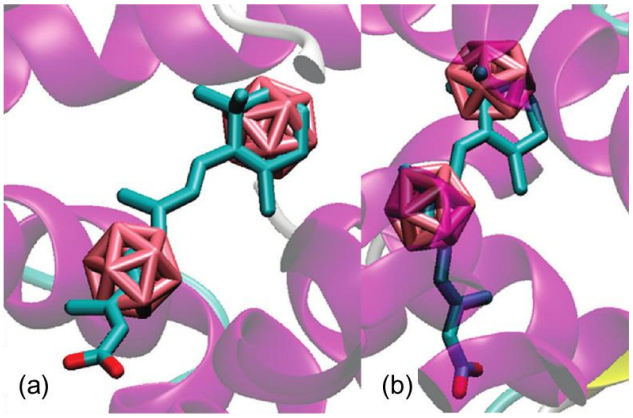


Figure 7. (a) Crystal structure of RAR with *trans*-retinoic acid superimposed with dicarba-*closo*-dodecarborane docking pose. (b) Crystal structure of RXR with *cis*-retinoic acid superimposed with dicarba-*closo*-dodecarborane docking pose. Reprinted with permission from ref. 55. Copyright (2011) American Chemical Society.

The experimental results of Endo along with the simulations of Calvaresi and Zerbetto suggest that dicarba-*closo*-dodecarborane derivatives could be used in the development of selective agonists or antagonists of RARs and RXRs.

1.D.2. Kinases and proteases.

The human genome encodes 518 kinases. The active sites of these kinases possess similar structures and sequences but the regulation of their catalytic activity differs. On the other hand, perturbations of protein kinase-mediated cell signalling pathways are observed in cancers, diabetes and inflammations.[56] Thus, modulation of kinase activity is of major importance.

Interest in using dicarba-*closo*-dodecarboranes as pharmacophore to target kinases was pioneered in 1999 by Endo and co-workers, with the synthesis of benzolactam molecules bearing dicarba-*closo*-dodecarborane units and acting as protein kinase C modulators.[57] These compounds mimic the active conformation and structure of teleocidins that are potent tumour promoters able to activate protein kinase C,[58] and induce growth inhibition and cell adhesion.[59] The high activity found for these dicarba-*closo*-dodecarborane-containing benzolactams indicate that they possess the requisite structures for hydrogen-bonding and hydrophobic interaction with protein kinase C. Docking simulations were also performed and matching structures between ligands and protein kinase C CRD2 domain were found.[57]

Potential biological applications of dicarba-*closo*-dodecarboranes other than as nuclear receptor ligands, have been recently discovered by Calvaresi and Zerbetto.[55] They studied *in silico* ligand-protein molecular docking and database screening, potential interactions between dicarba-

closo-dodecarborane and various proteins. These docking experiments show that rho-associated kinase or thiamin pyrophosphokinase are potential protein target candidates for dicarba-*closo*-dodecarborane binding, among others. Thus dicarba-*closo*-dodecarborane-containing half-sandwich complexes could become a new generation of specific kinase modulators.

Protease enzymes are another class of potential targets for dicarba-*closo*-dodecarborane-containing molecules. Proteases catalyse the hydrolysis of peptide bonds and can play an important role for disease propagation. Their inhibitors could find applications in many treatments, such as cancer or neurodegenerative disorders.[60] The strong hydrophobic pharmacophore behaviour of dicarba-*closo*-dodecarboranes, the regioselectivity and ease of derivatisation of these molecules and their chemical stability and metabolic inertness make them attractive candidates for the inhibition of proteases. In particular some dicarba-*closo*-dodecarborane derivatives are currently in advanced stages of development as inhibitors of HIV protease.[61] The *in silico* recognition and binding of a basic residue inside a hydrophobic pocket (S_1) of the serine protease MBL-associated serine protease-2 (MASP-2) illustrates the ability of dicarba-*closo*-dodecarboranes to specifically bind some residues of proteases.[55] The docked complex of dicarba-*closo*-dodecarborane and MASP-2 is shown in Figure 8.

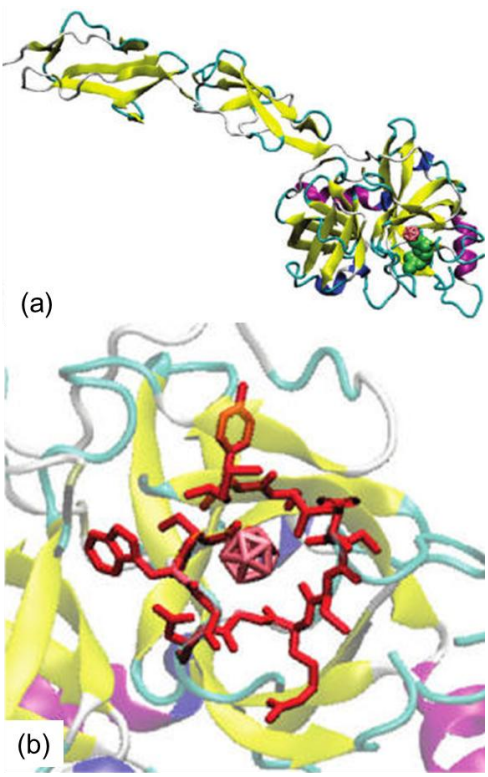


Figure 8. (a) Docked complex of a dicarba-*closo*-dodecarborane molecule and MASP-2. (b) Close-up of the dicarba-*closo*-dodecarborane binding pocket (S_1 site in red). Reprinted with permission from ref. 55. Copyright (2011) American Chemical Society.

1.E. To design anticancer drugs.

The combination of the demonstrated biological properties of half-sandwich complexes of ruthenium, osmium, rhodium and iridium[3-8] with the characteristics of dicarba-*closo*-dodecarboranes provides a promising basis for the design of new efficient anticancer agents. For example, confocal fluorescence microscopic studies have been performed with the ferrocene-containing ruthenium complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)] (see Figure 9 for the molecular structure of complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)]) in order to evaluate the effect of this complex on the uptake of the fluorescent daunorubicin drug into cancer cells (see Figure 10C for the molecular structure of daunorubicin).[62]

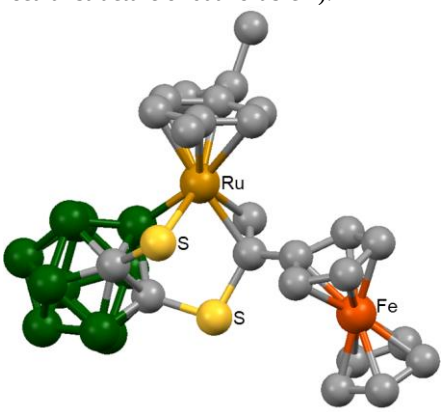


Figure 9. Molecular structure of ferrocene-containing ruthenium complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)].[62]

A weak fluorescence was observed when drug-resistant K562/ADM leukemia cells were incubated with daunorubicin alone. Moreover, this fluorescence was concentrated in the cell membranes, (see Figure 10A and 10a). However, when K562/ADM cells were incubated with a mixture of daunorubicin and non-fluorescent complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)] a strong fluorescence was observed indicating significant uptake of daunorubicin into the cells, (see Figure 10B and 10b). Figure 10D summarises these data with a superposition of the relative fluorescence intensity curves of 10a and 10b.

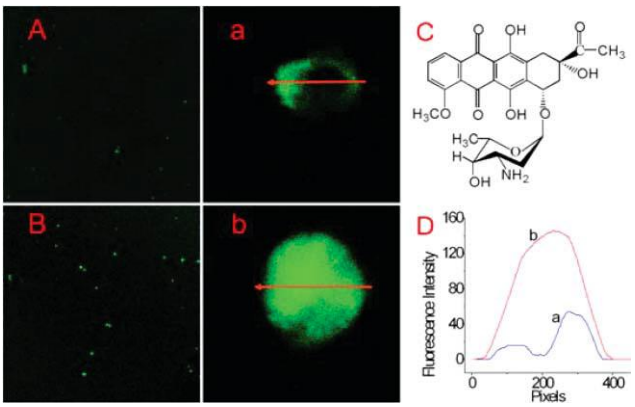


Figure 10. Confocal fluorescence microscopy of drug resistant K562 leukemia cells incubated with daunorubicin (180 μM) in the absence (A, a) and presence (B, b) of complex [*p*-

cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)] (14 mM). A and B represent panoramic images. a and b illustrate a typical single cell image from A and B, respectively. C shows daunorubicin. D indicates relative fluorescence intensity curves of a and b. All images were obtained after incubating the cells for 15 min. Reprinted with permission from ref. 62. Copyright (2009) Royal Chemical Society.

The increase in uptake of daunorubicin in the presence of complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)] was also confirmed by electrochemical studies. This enhancement of the uptake of daunorubicin was attributed to the ability of complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CCFc)$)] to enter into cancer cells and to affect the transportation or the signal regulation of daunorubicin related proteins such as P-glycoprotein (which is located on the surface of cells and prevents daunorubicin from entering the cells).

Yan and co-workers have also studied the cytotoxicity of complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CC(CO_2H))$)], (see Figure 11 for the molecular structure of complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CC(CO_2H))$)]).[63] The IC_{50} values of this complex toward SMMC-7721 cancer cell line and HELF normal cells have been determined. Interestingly, an IC_{50} of 42 μM has been found for this complex against SMMC-7721 cancer cells while no effect on the proliferation of HELF cells was observed. Therefore, complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CC(CO_2H))$)]) presents a good selectivity toward cancer cells and could potentially be a promising BNCT agent.

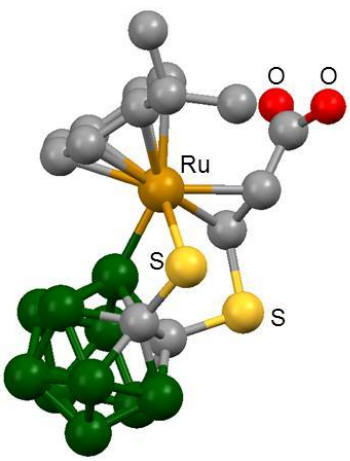


Figure 11. Molecular structure of mononuclear complex [*p*-cymRu($S_2C_2(B_{10}H_9)(H_2CC(CO_2H))$)].[63]

2. Synthesis of dicarba-*closo*-dodecarborane-containing half-sandwich complexes

2.A. *Ortho*-dicarba-*closo*-dodecarborane-1,2-dichalcogenolate ligands.

2.A.1. The 16-electron complexes precursors.

The first dicarba-*closo*-dodecarborane-containing half-sandwich complex of iridium was synthesised by Herberhold and co-workers in 1999 by reaction between dimeric pentamethylcyclopentadienyl (Cp*) iridium complex $[Cp^*IrCl_2]_2$ and dilithium *o*-dicarba-*closo*-dodecarborane -1,2-diselenolate in an ethanol/tetrahydrofuran mixture to give the corresponding 16-electron complex [Cp*Ir($Se_2C_2(B_{10}H_{10})$)] (**1**).[64] The same year the *o*-dicarba-*closo*-dodecarborane-1,2-dithiolate analogue was used to synthesise [Cp*Ir($S_2C_2(B_{10}H_{10})$)] (**2**).[65] This straightforward method was also applied to the dimeric pentamethylcyclopentadienyl rhodium complex $[Cp^*RhCl_2]_2$[66] and also to dimeric *para*-cymene ruthenium and osmium complexes[67] giving the corresponding 16-electron complexes [Cp*Rh($Se_2C_2(B_{10}H_{10})$)] (**3**), [Cp*Rh($S_2C_2(B_{10}H_{10})$)] (**4**), [*p*-cymRu($S_2C_2(B_{10}H_{10})$)] (**5**), and [*p*-cymOs($S_2C_2(B_{10}H_{10})$)] (**6**), respectively (see Figure 12 for the synthesis of **1** – **6**).

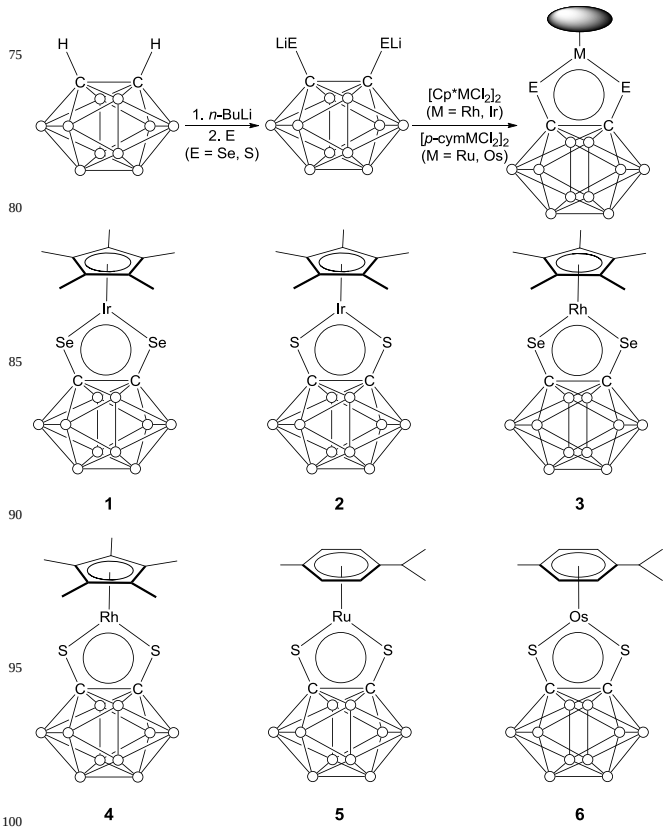


Figure 12. Synthesis of 16-electron complexes **1** – **6**.

Complexes **1** – **6** contain an almost planar pseudo-aromatic metalla-cycle MEC_2 (M = Ir, Rh, Ru, Os and E = Se, S). The steric hindrance due to the bulky *o*-dicarba-*closo*-dodecarborane-1,2-dichalcogenolate ligands prevents the dimerisation of these 16-electron complexes and formation of more stable 18-electron adducts.[68] Therefore, the monomer-dimer equilibrium reported for different dichalcogene 16-electron half-sandwich complexes[69] is not observed in these cases. The air-stable 16-electron complexes are particularly interesting as synthetic precursors since addition reactions can be carried out directly on the metal centre or insertion

reactions and B-H activation.

2.A.2. Addition reactions on the metal centre.

Numerous examples of addition reactions on the metal centre of complexes **1** – **6** have been reported: Herberhold and co-workers described the syntheses of coordinatively saturated 18-electron adducts obtained from precursors **1** – **6** and Lewis bases.[64-67] X-ray structure analyses show that the metalla-cycle MEC_2 is bent and that the pseudo-aromaticity is partially or totally lost upon addition reactions. This decrease of the symmetry order (C_{2v} –> C_s) was studied with complex **1** by addition of PMe_3, the resulting complex being $[Cp^*Ir(Se_2C_2(B_{10}H_{10}))(PMe_3)]$ (**7**).[64] An increase of 10 pm for the bond length Ir-Se (2.37 to 2.47 Å) in the solid state and a decrease of the Se-Ir-Se angle from 93.6° to 90.2° occurs for complex **7**, while the C_1-C_2 bond length increases from 1.61 to 1.65 Å, suggesting a loss of the pseudo-aromaticity of the MEC_2 metalla-cycle, (see Figure 13).

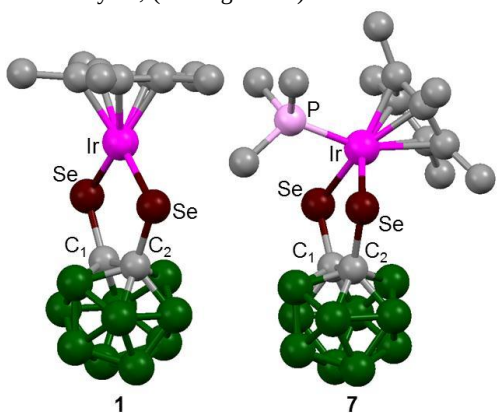


Figure 13. Molecular structures of mononuclear complexes **1** and **7**.[64]

Following the same strategy as for addition reactions, different electron donor molecules such as NH_3, CO, NC_5H_5, CN^-, SCN^-, SEt_2 and $P(OMe)_3$ have been used to convert 16-electron complexes **1** – **6** into their 18-electron congeners. The importance of the ligating atom of the Lewis base was established for complex **5** and with a decreasing stability order C > P > N > S > O.[67]

Addition reactions on the metal centres of complexes **1** – **6** can be used to synthesise multinuclear complexes.[70] Reactions between these 16-electron complexes and pyridinyl-based linear bidentate ligands such as pyrazine,[71] 4,4'-bipyridine,[71, 72] 1,2-di(4-pyridinyl)ethylene,[71] 4,4-azopyridine,[71b] di-isonicotinic acid 1,4-phenylene diester,[71b] *N,N'*-bis(4-pyridinylmethylene)biphenyl-4,4-diamine (bpbd),[71b] 2,5-bis(4-pyridyl)-1,3,5-oxadiazole,[71] and 2,6(7)-bis(4-pyridyl)-1,4,5,8-tetrathiafulvalene[72] as electron-donor molecules allow the formation of 18-electron dimeric complexes. Figure 14 illustrates an example of such dinuclear complexes with the molecular structure of $[(Cp^*Rh(S_2C_2(B_{10}H_{10})))_2(bpbd)]$ (**8**).[71b]

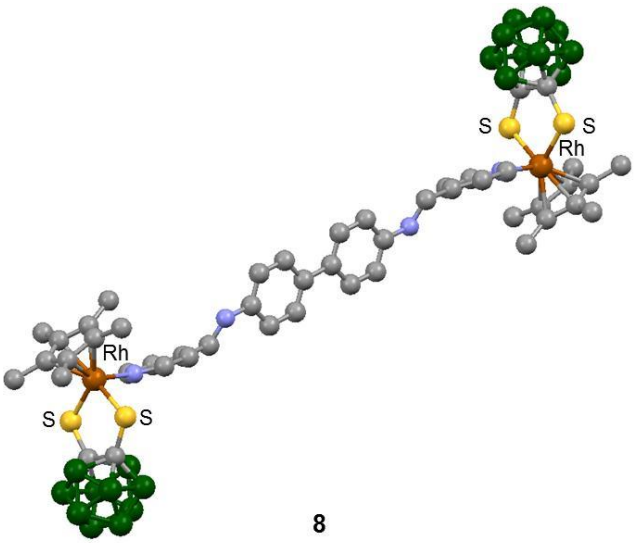


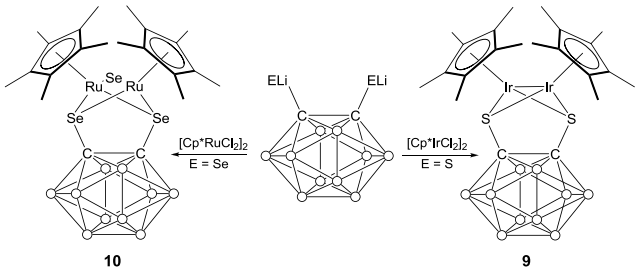
Figure 14. Molecular structure of the dinuclear complex **8**.[71b]

Trinuclear and tetranuclear complexes have also been synthesised from pyridinyl-based tridentate and tetradentate ligands:[70] 2,4,6-tris(4-pyridyl)-1,3,5-triazine[71b, 72, 73] and 5,10,15,20-tetra(4-pyridyl)porphyrin,[71b] for example, have been exploited as Lewis donor linkers.

2.A.3. Direct formation of metal-metal bonds.

Half-sandwich clusters of ruthenium, osmium, rhodium and iridium are useful and versatile molecules and find applications in various areas.[74] In particular, their potential as catalysts[75] or anticancer agents[76] has been explored. Hence, the rational design of direct metal-metal bond is a subject of major importance. In this context, the electronic deficiency of the metal centre in 16-electron complexes **1** – **6** leads to a remarkable synthetic ability for the formation of multimetallic complexes by creation of direct metal-metal (M–M') bonds.

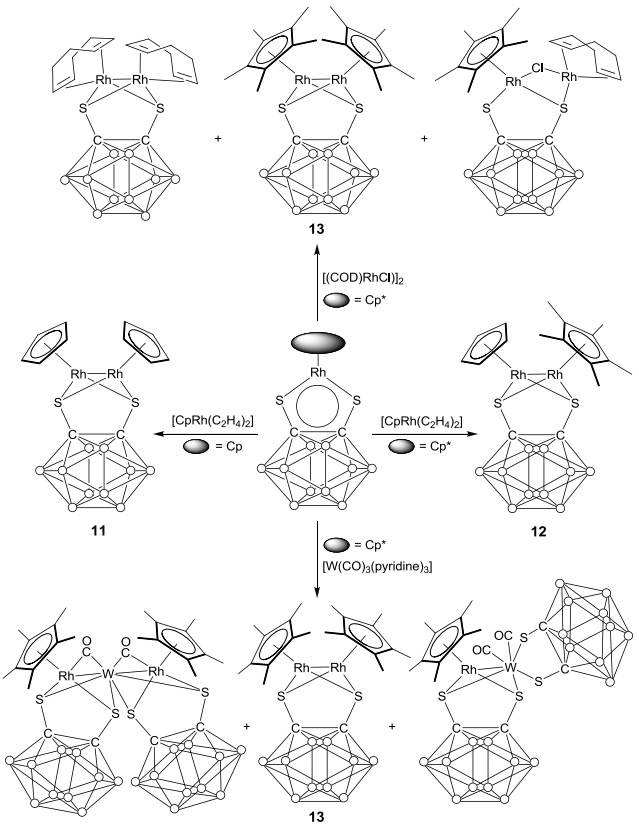
Different strategies can be employed to synthesise homo- and hetero-binuclear clusters containing half-sandwich complexes and ancillary *o*-dicarba-*closo*-dodecarborane-1,2-dichalcogenolate ligands. First, homo-binuclear complexes can be obtained as by-products from the synthesis of the 16-electron precursors **1** – **6** but this strategy leads to poor yields. For example, the synthesis of complex $[Cp^*_2Ir_2(S_2C_2B_{10}H_{10})]$ (**9**) by reaction between $[Cp^*IrCl_2]_2$ and *o*-dicarba-*closo*-dodecarborane-1,2-dithiolate has a yield of only 2%.[77] Interestingly, the same reaction with the 17-electron $[Cp^*RuCl_2]_2$ and with the *o*-dicarba-*closo*-dodecarborane-1,2-diselenolate analogous leads to the formation of a monoselenide bridge and to the isolation of complex $[Cp^*_2Ru_2(\mu\text{-}Se)[\mu\text{-}Se_2C_2(B_{10}H_{10})]$ (**10**) that does not possess a ruthenium-ruthenium bond, (see Scheme 1).[78]



Scheme 1. Syntheses of homo-binuclear complexes **9** and **10**.

Another approach consists of mixing the 16-electron precursors with low-oxidation-state complexes. This strategy has been extensively employed to construct Rh–Rh bonds and leads to better yields than the first strategy. For instance the rhodium binuclear cluster $[Cp_2Rh_2(S_2C_2B_{10}H_{10})]$ (**11**) is obtained with a yield of 49% by reaction between $[CpRh(C_2H_4)_2]$ and 16-electron precursor $[CpRh(S_2C_2B_{10}H_{10})]$ **4**, in toluene at 40°C, (see Scheme 2).[79] This procedure also allows the synthesis of complex $[(CpRh)(Cp^*Rh)(S_2C_2B_{10}H_{10})]$ (**12**) by reaction between precursor **4** and $[CpRh(C_2H_4)_2]$. This synthetic pathway leads to the isolation of the rhodium analogue of **9** $[Cp^*_2Rh_2(S_2C_2B_{10}H_{10})]$ (**13**) by reaction between precursor **4** and $[Rh(COD)Cl]_2$ (COD = 1,5-cyclo-octadiene) in dichloromethane.[80] In this case, complexes $[(COD)_2Rh_2(S_2C_2B_{10}H_{10})]$ and $[(Cp^*Rh)((COD)Rh)(Cl)(S_2C_2B_{10}H_{10}))]$ are also obtained, (see Scheme 2). Finally, compound **13** can also be synthesised by reaction between precursor **4** and $[W(CO)_3(pyridine)_3]$ in the presence of BF_3OEt_2. The reaction gives a mixture from which complex **11** is isolated with a yield of 16%.[81] The main product obtained in this reaction is the hetero-binuclear complex $[Cp^*Rh(S_2C_2(B_{10}H_{10}))\text{-}W(CO)_2(S_2C_2(B_{10}H_{10}))]$ (yield = 49%). The complex $[(Cp^*Rh(S_2C_2(B_{10}H_{10})))_2W(CO)_2]$ is also synthesised with a yield of 21%, (see Scheme 2).

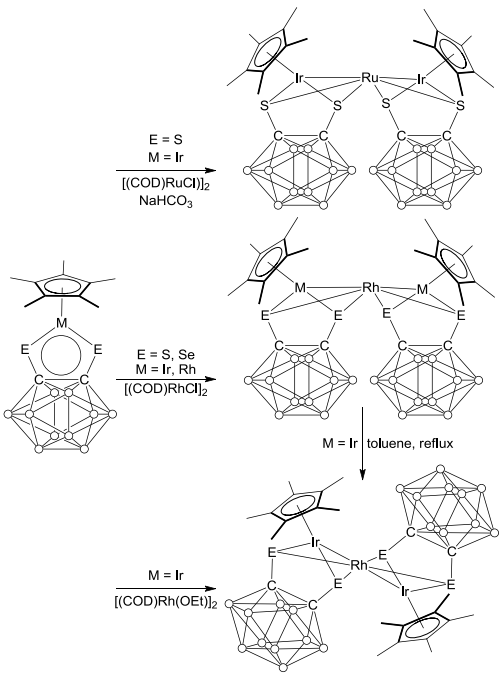
In all these reactions, reduction of Rh(III) to Rh(II) in complex **4** by $[CpRh(C_2H_4)_2]$, $[W(CO)_3]$ (generated by reaction between BF_3 and $[W(CO)_3(pyridine)_3]$), or $[Rh(COD)Cl]_2$ is observed. This facile approach has been applied to construct various homo-binuclear clusters containing half-sandwich complexes of rhodium. However the formation of Ir–Ir bonds *via* this strategy does not seem to be applicable due to a strong stabilisation of the complexes by Ir–B interactions.[80]



Scheme 2. Syntheses of homo-binuclear complexes of rhodium from 16-electron precursors.

This strategy has been generalised to the synthesis of hetero-binuclear clusters: various Rh–Ir, Rh–Ru and Ir–Ru bonds have been reported in clusters containing both half-sandwich complexes and *o*-dicarba-*closo*-dodecarborane-1,2-dichalcogenolate ligands.[80] Moreover, homo- and hetero-trinuclear clusters have also been synthesised from precursors **1** – **4** by reaction with $[Ru(COD)Cl]_2$ in the presence of $NaHCO_3$ and by reaction with $[Rh(COD)Cl]_2$ or $[Rh(COD)(\mu\text{-}OEt)]_2$, (see Scheme 3).[80]

Routes for the syntheses of homo- and hetero-multinuclear clusters from half-sandwich complexes and ancillary 1,2-dichalcogenolate dicarba-*closo*-dodecarborane ligands have been described.[80]



Scheme 3. Routes for the synthesis of homo- and hetero-trinuclear clusters from 16-electron precursors.

Concerning the behaviour of these clusters, the combination of the properties of the cyclopentadienyl and arene ligands with the characteristics of the dicarba-*closo*-dodecarborane units allows control of the solubility of the resulting molecules as well as of their polarity, chirality, redox properties and reactivity.[80] Moreover, the possibility to synthesise homo- or hetero-multinuclear clusters gives a large spectrum of readily accessible molecules with various structures and bonding situations. For example, important variations of the M–M' bond length are observed depending on the ligands that surround the different metal centres or depending on the geometry of the cluster.[82]

This structural versatility is illustrated by the conversion of *cis*-[(Cp*Ir($Se_2C_2(B_{10}H_{10})$))$_2$Rh] (**14**) to *trans*-[(Cp*Ir($Se_2C_2(B_{10}H_{10})$))$_2$Rh] (**15**) reported by Jin and co-workers.[83] In cluster **14**, a length of 2.7097(11) Å was found for the Ir_1–Rh bond, while in the isomer **15**, the Ir_1–Rh bond length is 3.074(3) Å, (see Figure 15).

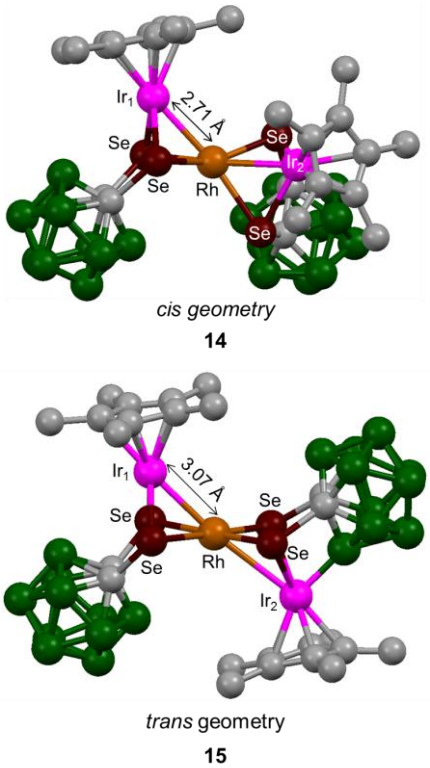


Figure 15. Molecular structures of *cis* and *trans* trinuclear isomers **14** and **15**.[83]

The nature of the ligands also has a crucial influence on the structures of the clusters. The role played by ligands is clearly illustrated in the complex [CpRh(Cp*Rh)($S_2C_2(B_{10}H_{10})$)] (**16**). Indeed, in the solid state, the metal-sulphur bond in Cp*Rh-S is slightly longer than in CpRh-S (2.3344(11) Å *versus* 2.3256(11) Å), (see Figure 16).[79] This structural difference has been attributed to the higher electron density of the Cp* ligand as compared to Cp.

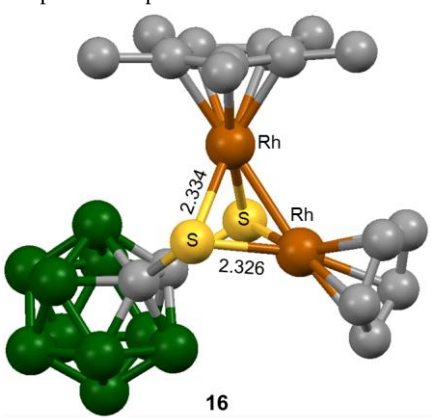
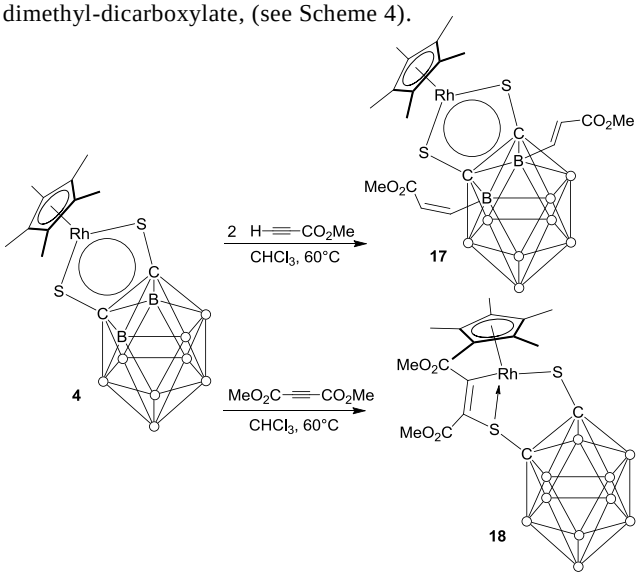


Figure 16. Molecular structure of dinuclear complex **16**.[79]

2.A.4. B−H activation.

B−H activation, *ortho*-metallation and B(3,6)-substitution of the *o*-dicarba-*closo*-dodecarborane cluster have been extensively used to functionalise dicarba-*closo*-dodecarborane-containing half-sandwich complexes of

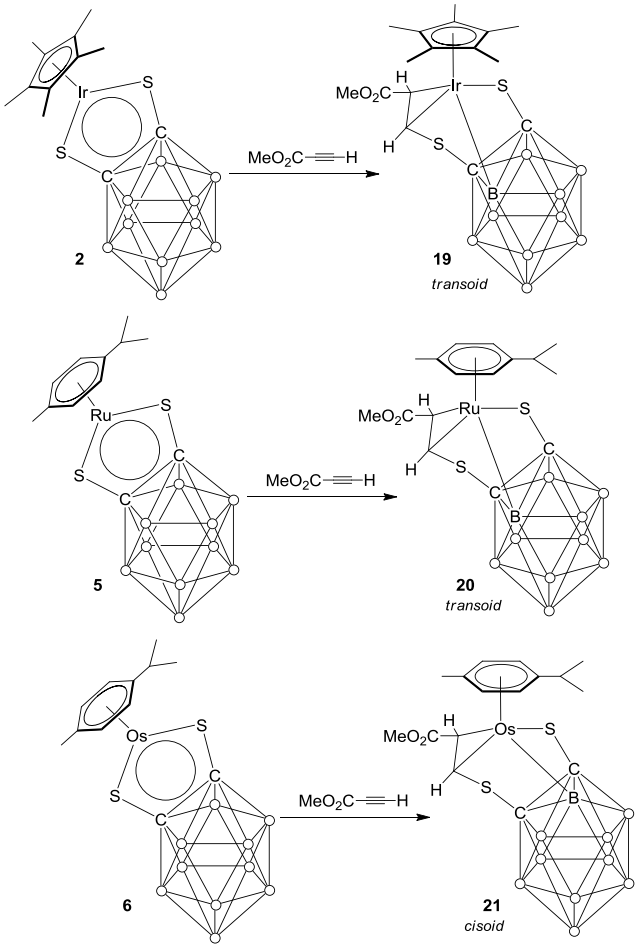
ruthenium, osmium, rhodium and iridium. Herberhold and co-workers reported in 1999 reactions between precursor **4** and acetylene methyl carboxylate and acetylene dimethyl-dicarboxylate.[84] The formation of a stable 16-electron complex (**17**) was observed in the first case while a 18-electon complex (**18**) was obtained by reaction of **4** with acetylene dimethyl-dicarboxylate, (see Scheme 4).



Scheme 4. Reaction of precursor **4** with mono and disubstituted acetylenes to give complexes **17** and **18**.

The authors suggested that the 18-electron complex **18** has the typical structure of a reaction intermediate. This intermediate is stable and can be isolated on reaction of the disubstituted acetylene with **4** but is not detectable when the monosubstituted acetylene reacts. This hypothesis led to the suggestion of a mechanistic pathway in-which the geometry of the 18-electron intermediate allows the approach of the metal atom to the sites of either B(3)−H or B(6)−H resulting in B−H activation.[85] Hydride transfers from boron to rhodium and then from rhodium to the olefinic carbon atom followed by the cleavage of the boron−metal bond lead to the substitution of the dicarba-*closo*-dodecarborane cluster in positions B(3) and B(6). Thus the reactivity of the metal centre, the metal-sulphur bond and the B(3,6)−H bond are involved in the reactions between precursor **4** and unsaturated substrates.

Analogous reactions between acetylene methyl carboxylate and precursors **2**, **5** and **6** also provide evidence for B−H activation.[86] Compounds **19**, **20** and **21** have been obtained with a *cisoid* geometry for complex **21** and a *transoid* geometry for complexes **19** and **20**. The B−C(1) bond and the η^2-(S)CH=CH bond are oriented in the same direction in the coordination sphere of the metal centre in a *cisoid* geometry and in the opposite direction in a *transoid* geometry, (see Scheme 5). These compounds are stable and do not undergo further rearrangements. Therefore, the B(3,6)-substitution of the *o*-dicarba-*closo*-dodecarborane cluster is not observed with the iridium, ruthenium and osmium analogues of rhodium precursor **4**.



Scheme 5. Syntheses of complexes **19**, **20** and **21**.

This synthetic strategy has been applied to various acetylene derivatives. For instance, the reaction between precursor **1** and phenylacetylene leads to the synthesis of the *cisoid* 18-electron complex **22**, (see Figure 17).[87]

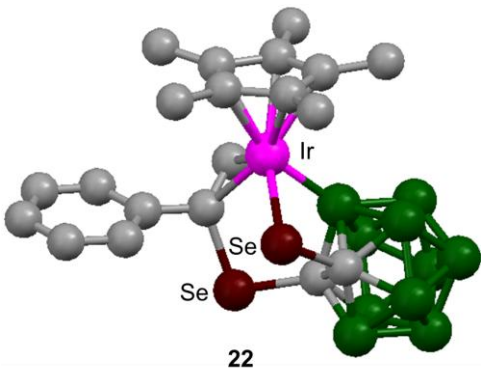


Figure 17. Molecular structure of *cisoid* mononuclear complex **22**.[67]

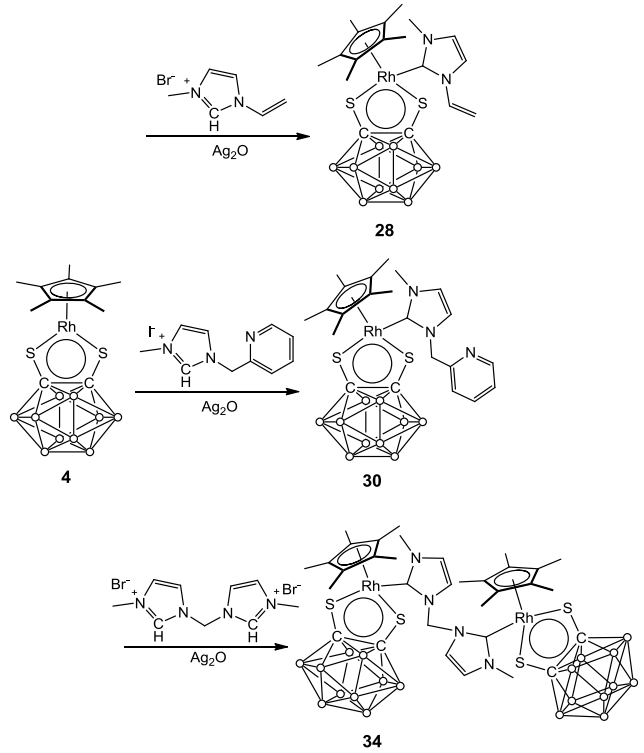
More recently, Yan and co-workers reported the addition of ethynylferrocene to precursors **1**, **2**, **5** and **6** leading to the *cisoid* 18-electron complexes [Cp*Ir(Se_2C_2($B_{10}H_9$)(H_2CCFc))] (Fc = ferrocenyl) (**23**), [Cp*Ir(S_2C_2($B_{10}H_9$)(H_2CCFc))] (**24**), [*p*-cymRu(S_2C_2($B_{10}H_9$)(H_2CCFc))] (**25**) and [*p*-cymOs(S_2C_2($B_{10}H_9$)(H_2CCFc))] (**26**), respectively.[62] The

molecular structure of complex **25** is shown in Figure 9.

The same research group studied recently the reactivity of the 16-electron precursor **5** towards a series of diynes.[69] Interestingly, most of these reactions led to the isolation of mononuclear complexes containing a stable Ru−B bond. Only a binuclear complex was isolated during the reaction of **5** with 2,5-diethynylthiophene. With the other diynes (1,4-diethynylbenzene, 3',6-diethynyl-1,1'-binaphthyl-2,7'-diyl diacetate and 2-bromo-5-ethynylthiophene) the reactivity of the second alkynyl group is inhibited. Electronic rather than steric effects play a key role in the generation of such binuclear complexes.[88]

2.A.5. Transmetalation.

Functionalization of the 16-electron complexes **1** − **6** with *N*-heterocyclic carbene (NHC) derivatives can be readily achieved by silver carbene transfer. The reactions of mono- or di-carbenes with these precursors give either 18-electron mononuclear or 18-electron binuclear complexes. To illustrate these transmetalation reactions, Jin and co-workers reacted precursors **2**, **3**, **4** and **5** with 1-ethenyl-3-methylimidazolium bromide, 3-methyl-1-picolyimidazolium iodide and 1,1'-dimethyl-3,3'-methylenediimidazolium dibromide in the presence of silver oxide.[89] Corresponding complexes [Cp*Ir($S_2C_2B_{10}H_{10}$)(1-ethenyl-3-methylimidazolin-2-ylidene)] (**27**), [Cp*Rh($S_2C_2B_{10}H_{10}$)(1-ethenyl-3-methylimidazolin-2-ylidene)] (**28**), [*p*-cymRu($S_2C_2B_{10}H_{10}$)(1-ethenyl-3-methylimidazolin-2-ylidene)] (**29**), [Cp*Rh($Se_2C_2B_{10}H_{10}$)(3-methyl-1-picolyimidazolin-2-ylidene)] (**30**), [Cp*Rh($S_2C_2B_{10}H_{10}$)(3-methyl-1-picolyimidazolin-2-ylidene)] (**31**), [*p*-cymRu($S_2C_2B_{10}H_{10}$)(3-methyl-1-picolyimidazolin-2-ylidene)] (**32**), [(Cp*Ir($S_2C_2B_{10}H_{10}$))$_2$(1,1'-dimethyl-3,3'-methylene(imidazolin-2-ylidene))] (**33**) and [(Cp*Rh($S_2C_2B_{10}H_{10}$))$_2$(1,1'-dimethyl-3,3'-ethylene(imidazolin-2-ylidene))] (**34**) were obtained in good yields (64−86%). The reactions between precursor **4** and the three NHC ligands are shown in Scheme 6.



Scheme 6. Synthesis of complexes **28**, **30** and **34**.[89]

This *in situ* transmetalation reaction between a solution of the Ag-carbene complex and a 16-electron precursor has also been employed to synthesise trinuclear half-sandwich transition-metal complexes [(Cp*Ir($E_2C_2B_{10}H_{10}$))$_3$(tris(2-(3-methylimidazol-2-ylidene)ethyl)amine)] (E = Se (**35**), S (**36**)) and [(Cp*Rh($E_2C_2B_{10}H_{10}$))$_3$(tris(2-(3-methylimidazol-2-ylidene)ethyl)amine)] (E = Se (**37**), S (**38**)) containing both NHC and *o*-dicarba-*closo*-dodecarborane-1,2-dichalcogenolate ligands.[90] These complexes can also be synthesised by reaction of [(Cp*MCl_2)$_3$(tris(2-(3-methylimidazol-2-ylidene)ethyl)amine)] with $Li_2Se_2C_2B_{10}H_{10}$ (E = Rh, Ir). The molecular structure of complex **36** is shown in Figure 18.

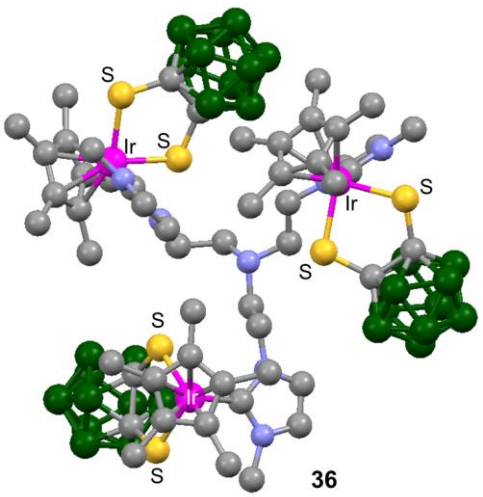


Figure 18. Molecular structure of trinuclear complex **36**.[90]

2.B. Functionalised *para*-dicarba-*closo*-dodecarborane ligands.

Whilst the sulphur and selenium *o*-dicarba-*closo*-dodecarborane-1,2-dichalcogenolate molecules are coordinated to the metal atoms in the vast majority of the reported dicarba-*closo*-dodecarborane-containing half-sandwich complexes of ruthenium, osmium, rhodium and iridium, a few examples of other dicarba-*closo*-dodecarborane derivatives employed as ligands can be found in the literature. Among them, the cases of the C,C'-bis(ethynyl)-*p*-dicarba-*closo*-dodecarboranes are noteworthy. In 2008, Low and co-workers studied reactions between the cyclopentadienyl ruthenium complex [Cp*Ru(dppe)Cl] (dppe = 1,2-bis(diphenylphosphino)ethane) and two *para*-dicarba-*closo*-dodecarborane molecules functionalised on C-H vertices: 1-$Me_3SiC{\equiv}C$-1,12-$C_2B_{10}H_{11}$ (**39**), and 1,12-$(Me_3SiC{\equiv}C)_2$-1,12-$C_2B_{10}H_{10}$ (**40**), (see Figure 19).[91] These ligands combine the physical and electronic properties of the *p*-dicarba-*closo*-dodecarborane units with one or two ethynyl groups. The degree of electronic communication between the axial substituents of the dicarba-*closo*-dodecarborane cage **40** can be compared to the electronic communication between axial substituents of *para*-substituted benzenes.[92]

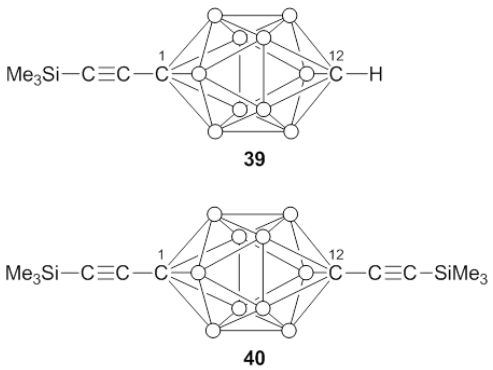


Figure 19. Structures of ligands **39** and **40**.

The syntheses of the two resulting complexes were carried out in methanol at reflux in the presence of KF and led in good yields of the mono- and bi-metallic acetylide complexes featuring dicarba-*closo*-dodecarboranes embedded within the mono-ethynyl ligands and the di-ethynyl bridging ligands: [Cp*Ru(dppe)(1-C≡C-1,12-$C_2B_{10}H_{11}$)] (**41**), and [$(Cp^*Ru(dppe))_2$(μ-1,12-$(C{\equiv}C)_2$-1,12-$C_2B_{10}H_{10}$)] (**42**).[91] The molecular structure of complex **42** is shown in Figure 20.

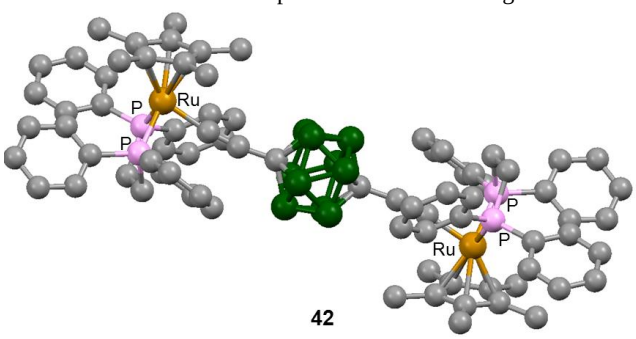
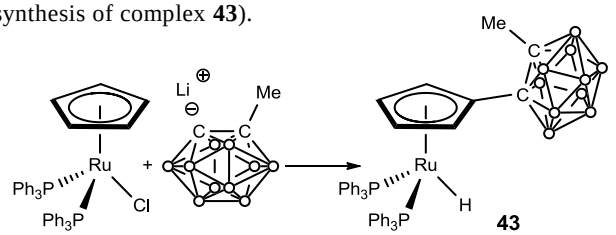


Figure 20. Molecular structure of dinuclear complex **42** showing the di-ethynyl dicarba-*closo*-dodecarborane-containing bridging ligand.[91]

2.C. Functionalised *ortho*-dicarba-*closo*-dodecarborane ligand.

Just as the functionalization of *para*-dicarba-*closo*-dodecarborane can lead to the synthesis of new ligands that enhance the degree of electronic communication between two metal centres, the functionalization of *ortho*-dicarba-*closo*-dodecarborane can also give rise to new and interesting ligands. As an example, in order to improve the reactivity of cyclopentadienyl ruthenium(II) complexes toward substitution, Basato and co-workers studied in 2004 the reaction between the complex [$CpRu(PPh_3)_2Cl$] and the deuterated analogous [$(C_5D_5)Ru(PPh_3)_2Cl$] with an ethereal solution of the bulky and poor electron-withdrawing anion 2-Me-*o*-dicarba-*closo*-dodecarborane ($MeC_2B_{10}H_{10}^-$, Li^+ synthesised by reaction between 2-Me-*o*-dicarba-*closo*-dodecarborane and *n*-BuLi) in toluene.[93] Nucleophilic attack of $MeC_2B_{10}H_{10}^-$ on the cyclopentadienyl ring was observed instead of a more expected exchange between the chloride ligand and the 2-Me-*o*-dicarba-*closo*-dodecarborane anion affording hydrido complexes [(C_5H_4-$MeC_2B_{10}H_{10}$)$Ru(PPh_3)_2H$] (**43**) and [(C_5D_4-$MeC_2B_{10}H_{10}$)$Ru(PPh_3)_2D$] (**44**), (see Scheme 7 for the synthesis of complex **43**).



Scheme 7. Synthesis of complex **43**.[93]

To determine the role played by the spectator ligands on the substitution site, Basato and co-workers published in 2007 a series of reactions between the 2-Me-*o*-dicarba-*closo*-dodecarborane anion and a number of ruthenium cyclopentadienyl complexes characterised by different sets of neutral ligands, [$CpRu(L_1L_2)Cl$] (L_1, L_2 = PMe_2Ph, $PMePh_2$; dppe; 1,5-cyclooctadiene (COD); CO, PPh_3).[94] Depending on the nature of L_1L_2 spectator ligands, a substitution on the cyclopentadienyl ring (L_1, L_2 = COD; CO, PPh_3) or on the metal centre (L_1, L_2 = PMe_2Ph, PMe_2Ph; $PMePh_2$, $PMePh_2$; dppe) is observed. This difference of substitution site appears to be related to steric effects, since for the less hindering phosphine ligands ($PMePh_2$ *versus* PPh_3) an exchange between the chlorido ligand and the 2-Me-*o*-dicarba-*closo*-dodecarborane anion took place.

Electronic effects also play a role. Indeed, the reaction between [$CpRu(PPh_3)(CO)Cl$] (where a bulky PPh_3 is replaced by a small CO ligand) and the 2-Me-*o*-dicarba-*closo*-dodecarborane anion leads to attack on the cyclopentadienyl ring. Therefore, based on electrochemical studies of [$CpRu(L_2)Cl$] complexes,[95] it was concluded that the presence of poor electron-donor ligands such as CO or COD decreases

the electron density on the metal and thus on the coordinated cyclopentadienyl ring, leading to nucleophilic attack on the Cp ligand. Figure 21 illustrates the two possible substitution sites for the molecular structures of complex [(C_5D_4-$MeC_2B_{10}H_{10}$)Ru(PPh_3)$_2$D] (**44**) and complex [CpRu(PMe_2Ph)$_2$($MeC_2B_{10}H_{10}$)] (**45**).

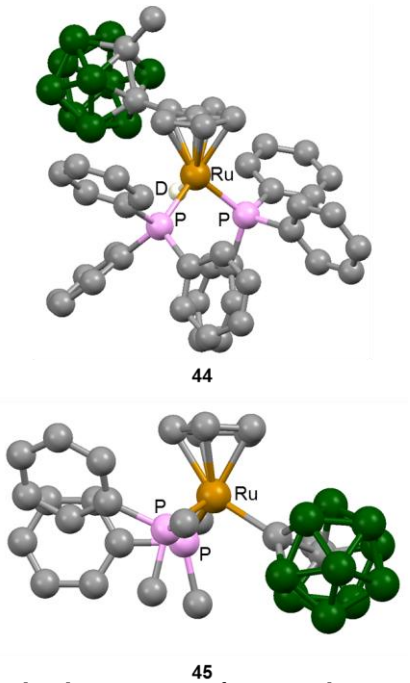
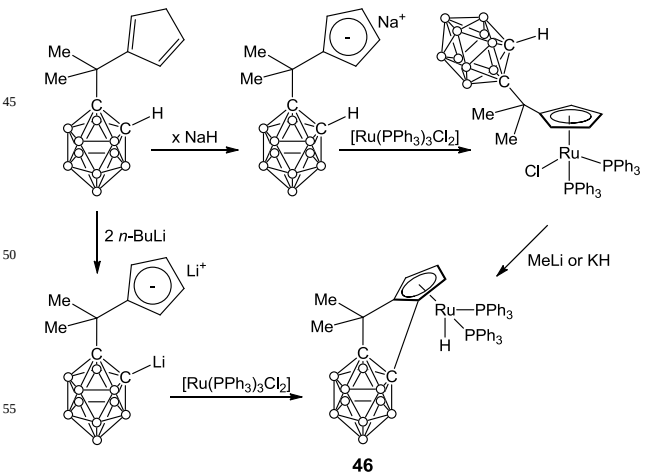


Figure 21. Molecular structures of mononuclear complexes **44** and **45**.[93, 95]

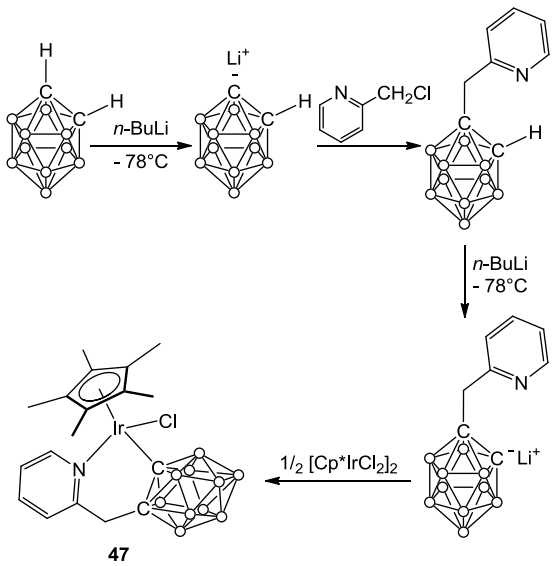
At the same time, Xie and co-workers published in 2004 another dicarba-*closo*-dodecarborane-containing half-sandwich complex of ruthenium in which the cyclopentadienyl ring is functionalized with a dicarba-*closo*-dodecarborane moiety.[96] They grafted a cyclopentadienyl unit onto a dicarba-*closo*-dodecarborane molecule and then reacted this cyclopentadienyl-carboranyl compound ($Me_2C(C_5H_5)$-$C_2B_{10}H_{10}$) with [Ru(Cl)$_2$(PPh_3)$_3$]. The hydrido complex [($Me_2C(C_5H_3)$)Ru(PPh_3)$_2$($C_2B_{10}H_{10}$)H] (**46**) was obtained in good yield, (see Scheme 8).



Scheme 8. Synthesis of complex **46**.[96]

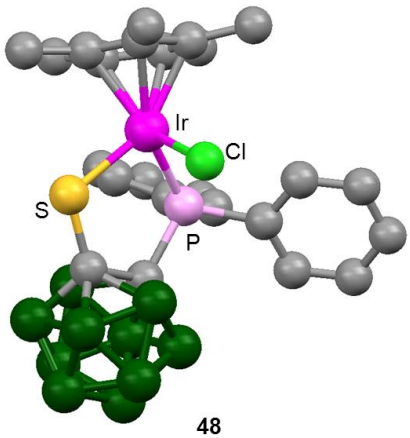
In 2006, the same authors published an extension of this work in-which a series of cyclopentadienyl-carboranyl half-sandwich complexes of ruthenium was synthesised following the same strategy.[97] Based on different examples, they showed that the coupling reaction of the Cp ring with the dicarba-*closo*-dodecarborane derivative requires the absence of a substituent on one of the carbon atoms of the cyclopentadienyl unit. Moreover, the presence of a triphenylphosphine coordinated to the metal atom is essential, which indicates a mechanism based on sterically-induced coupling.

Jin and co-workers also extensively used the functionalization of *o*-dicarba-*closo*-dodecarborane ligands to synthesise new dicarba-*closo*-dodecarborane-containing half-sandwich complexes. As an example, in 2005, they synthesised an half-sandwich picolyl-functionalized *ortho*-dicarba-*closo*-dodecarborane-containing complex of iridium.[98] The iridium complex [Cp*Ir($C_2B_{10}H_{10}CH_2C_5H_4N$)Cl] (**47**) was prepared by the reaction of 1-(2'-picolyl)-*o*-dicarba-*closo*-dodecarborane ($HC_2B_{10}H_{10}CH_2C_5H_4N$) with the dimeric metal complex [Cp*IrCl$_2$]$_2$, (see Scheme 9). The stability of this type of complex is attributed to the formation of a six-membered chelate ring.



Scheme 9. Synthesis of complex **47**.[98]

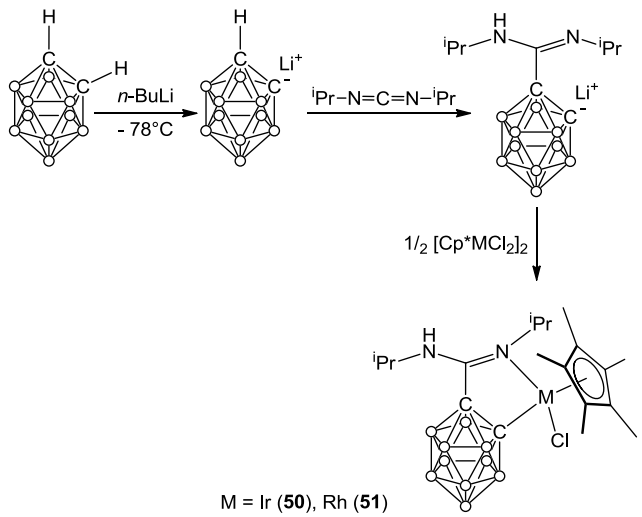
In 2010, the same group published the syntheses of neutral P,S-substituted *o*-dicarba-*closo*-dodecarborane-containing half-sandwich complexes of rhodium and iridium.[99] The reaction between [Cp*MCl$_2$]$_2$ (M = Ir, Rh) and two equivalents of the functionalised *o*-dicarba-*closo*-dodecarborane 1-PPh_2-2-LiS-1,2-$C_2B_{10}H_{10}$ gives the neutral P,S-chelated metal complexes [Cp*M(Cl)(1-PPh_2-2-S-1,2-$C_2B_{10}H_{10}$)] (M = Ir (**48**), Rh (**49**)), (see Figure 22 for the molecular structure of complex **48**).



48

Figure 22. Molecular structure of complex mononuclear complex **48**.

Finally, in 2011, the functionalization of *o*-dicarba-*closo*-dodecarborane by amidine derivatives led to the isolation of 18-electron half-sandwich complexes of rhodium and iridium containing carboranylamidinate ligands.[100] These carboranylamidinate ligands possess interesting properties[101] and their combination with different transition metals has given rise to complexes presenting potential in various domains such as catalysis,[102] and materials science.[103] Therefore the combination of carboranylamidinate ligands and half-sandwich complexes of ruthenium, osmium, rhodium and iridium is a new and attractive field to explore. In this context, the synthesis of the 18-electron complexes [Cp*M(^{i}PrN=C(*closo*-1,2-$C_2B_{10}H_{10}$)(NH^{i}Pr))Cl] (M = Ir (**50**), Rh (**51**)) by *in situ* formation of the C-lithiocarboranylamidinate ligand, followed by the addition of dimeric metal complex [Cp*$MCl_2]_2$ (M = Ir, Rh) in THF at room temperature represents an example of such a combination, (see Scheme 10).



Scheme 10. Synthesis of complexes **50** and **51**.

Conclusions

It is clear that dicarba-*closo*-dodecarborane derivatives can give rise to interesting and unusual properties as ligands in organometallic complexes. These clusters are remarkably stable in biological medium and can be recognised by various bio-targets. They can be easily functionalised *via* organic reactions on the CH vertices and they have useful probe properties. Due to the high number of boron atoms in their globular structures, they have been extensively studied as potential BNCT agents. Different clinical trials have been carried out in Japan, Europe, and the United States and sodium borocaptate ($Na_2B_{12}H_{11}SH$) has been used clinically. Nevertheless, selective and effective delivery of boron agents is still a critical issue. For this reason it is of central importance to explore new concepts able to take advantage of these unique pharmacophores. The combination of dicarba-*closo*-dodecarboranes with half-sandwich complexes of ruthenium, osmium, rhodium and iridium could provide the expected breakthrough in the dicarba-*closo*-dodecarborane biochemistry. The synthetic pathways described in this review illustrate the numerous strategies that can be employed to design dicarba-*closo*-dodecarborane-containing half-sandwich complexes. Addition reactions on the metal centre, B–H activation, transmetalation or functionalization of the cluster cages are some examples of such strategies. The properties of these dicarba-*closo*-dodecarborane-containing complexes have already allowed their utilisation in organometallic synthesis and biology. However this field of research is relatively recent and new developments and diversification can be expected in the near future.

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Notes and references

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